Pharmacologic, Pharmacokinetic, and Therapeutic Differences Among Angiotensin II Receptor Antagonists

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Over the past 4 years, six angiotensin II receptor antagonists (ARBs) were approved for treating essential hypertension. They differ with respect to dosing, metabolism, elimination, clinical efficacy, and investigational applications. Candesartan cilexetil is the only prodrug among the agents. Losartan is distinguished from other ARBs by cytochrome P450 (CYP) 3A4- and CYP2C9-mediated biotransformation to its active metabolite EXP-3174. No ARB requires dosage adjustment for renal impairment, but the initial dose of losartan should be reduced 50% in hepatically impaired patients. None of the drugs is significantly cleared by hemodialysis. Completion of continuing trials will elucidate the drugs' role in treating heart failure, cerebral stroke, and myocardial infarction.
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OUTLINE

Angiotensin-converting enzyme (ACE) inhibitors have been available to block the renin-angiotensin-aldosterone system (RAAS) for 15 years.[1] Numerous clinical trials established them as efficacious in treating patients with hypertension, congestive heart failure, myocardial infarction, and diabetic nephropathy.[2] An estimated 5–10% of patients taking ACE inhibitors develop a dry cough.[3] Because the RAAS plays a pivotal role in the pathogenesis of hypertension, congestive heart failure, and diabetic nephropathy, researchers have searched for alternative routes in blocking the RAAS that would avoid adverse effects associated with ACE inhibitors.[1, 4] Since April 1995, six nonpeptide angiotensin II receptor blockers (ARBs) were approved by the Food and Drug Administration (FDA) to treat hypertension: losartan, valsartan, irbesartan, candesartan, eprosartan, and telmisartan.[1, 3] Understanding the differences among ARBs will simplify selection of the most appropriate agent.

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Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is a critical component in regulating blood pressure, electrolyte balance, and fluid volume homeostasis.[5, 6] Renin release from juxtaglomerular cells located in renal afferent

arterioles begins the RAAS cascade. Factors triggering renin release include reduced perfusion pressure, decreased sodium chloride delivery to the distal tubule, and the direct action of catecholamines on β_1-receptors occupying juxtaglomerular cells.[7]

Renin, a 340 amino acid glycoprotein, is synthesized and stored in juxtaglomerular cells. After its release, it cleaves the decapeptide angiotensin I from circulating glycoprotein angiotensinogen.[8] Angiotensin I has minimal biologic activity and serves as a substrate for plasma or tissue aminopeptidases and ACE. Aminopeptidases act on angiotensin I to form [des-Asp^1] angiotensin I, which is converted to angiotensin III by ACE. Angiotensin-converting enzyme cleaves a dipeptide sequence from angiotensin I to yield the octapeptide angiotensin II.

Angiotensin II exerts its physiologic actions at numerous sites in the body, including vascular smooth muscle, adrenal cortex, kidneys, and brain.[9] Consequently, it is a key regulator of blood pressure and extracellular volume. Briefly, angiotensin II-mediated vasoconstriction of efferent arterioles and increased epinephrine release from the adrenal medulla both contribute to elevating blood pressure. Angiotensin II controls intravascular volume by promoting synthesis and release of aldosterone from the adrenal cortex, which increases proximal tubular sodium reabsorption. Other effects are thirst stimulation, decreased renin secretion, increased antidiuretic hormone secretion from the central nervous system, and mitogenesis of cardiac and vascular muscle cells.[2–6, 8]

Pharmacologic inhibition of the RAAS can occur by blocking renin secretion, renin action, and angiotensin II receptors, and by converting angiotensin I to angiotensin II. Renin secretion can be inhibited by β-blockers acting on juxtaglomerular cell β-receptors. Renin inhibitors interfere with formation of angiotensin I from angiotensinogen by competitively binding to active sites on renin. Renin inhibitors are available only for research due to their limited bioavailability and potential for disrupting the negative feedback effect of angiotensin II on renin secretion.[8] The ACE inhibitors halt formation of angiotensin II from angiotensin I by the converting enzyme. In addition, they block degradation of the potent vasodilator bradykinin and substance P. Despite the potential clinical benefits of bradykinin, bradykinin and substance P accumulation were postulated to be responsible for the cough associated with ACE inhibitors.[10]

Angiotensin II can be generated by other

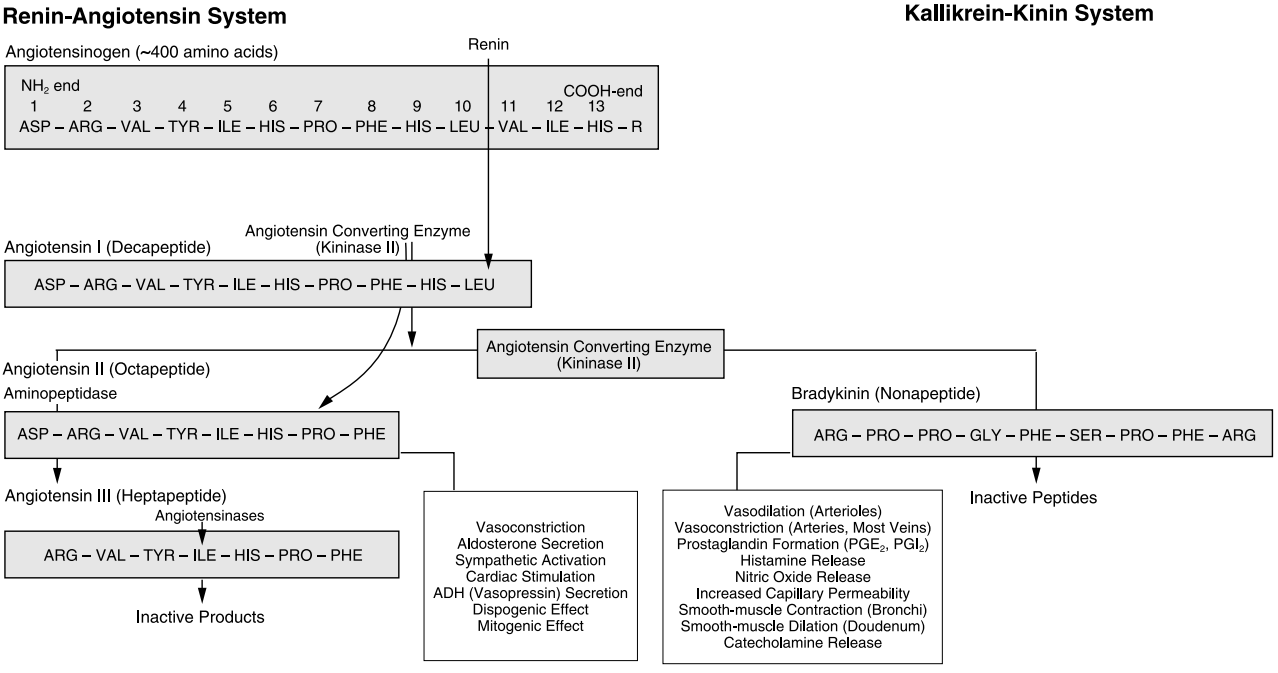

Figure 1. The biochemistry and physiology of the renin-angiotensin and kallikrein-kinin systems. Series of enzymatic reactions initiated by renin. Reprinted from reference 11 with permission.

enzymes including cathepsin G, elastase, tissue plasminogen activator, chymostatin-sensitive angiotensin II generator enzyme, and chymase.[2, 3, 5, 6] Because ACE inhibitors may not provide complete suppression of angiotensin II generation, angiotensin II receptor blockade offers the advantage of inducing absolute inhibition of angiotensin II activity. Angiotensin II receptors exist as subtype 1 (AT_1) and subtype 2 (AT_2), with AT_1 being responsible for the angiotensin II-mediated effects described above. The function of the AT_2 receptor has not been elucidated.[3–6] The six FDA-approved nonpeptide AT_1 receptor antagonists do not interrupt bradykinin metabolism and thus are unlikely to induce cough.[1] Figure 1 provides an overview of the RAAS.[2, 11]

Pharmacologic Differences

Chemical Structure

Most ARBs are characterized by having biphenyl, tetrazole, benzimidazole, or nonbiphenyl nontetrazole groups. Valsartan has a biphenyl group; agents with biphenyl and tetrazole-substituted imidazole groups are losartan, candesartan, and irbesartan. Telmisartan is a substituted benzimidazole derivative; eprosartan has a nonbiphenyl, nontetrazole-substituted imidazole group.[12, 13] It is unclear whether these structural differences will be translated into clinically significant effects, but more research is required.

Inhibition of Angiotensin II Activity

The AT_1 receptor is a polypeptide chain that traverses the cell membrane 7 times. Six amino acids from transmembrane domains III, IV, V, VI, and VII play a critical role in binding losartan.[14] The Ca-phosphoinositide signaling pathway is triggered by binding ARB to an AT_1 receptor. Briefly, G protein activation proceeds after formation of the AT_1 receptor-ARB complex, leading to phospholipase C stimulation. Phospholipase C then cleaves phosphatidyl inositol-4,5 bisphosphate to form inositol trisphosphate and diacylglycerol. Inositol trisphosphate releases calcium from the endoplasmic reticulum, thus inducing vascular contraction.[4]

In recent years, research efforts have been directed toward characterizing the binding of ARBs to the AT_1 receptor. Of special interest is classification of ARBs' AT_1-blocking capacity into two categories, insurmountable and surmountable. Insurmountable antagonism indicates suppression of agonist response despite escalations in agonist concentration. The reverse holds true for surmountable antagonism.[15] Since the AT_1 receptor is the dominant angiotensin II subtype in rabbit aorta and rat portal vein, in vitro research often is conducted using these animal models. To determine whether or not an ARB can exert insurmountable blockade, animal vascular preparations are exposed to increasing concentrations of angiotensin II until maximum contraction occurs. Incubation of the tissue with the ARB precedes repeat exposure to angiotensin II. The data are plotted on graphs where maximum contractile response represents the ordinate, and logarithms of angiotensin II concentrations represent the abscissa. A parallel shift to the right of the concentration-response curve, without significant depression in maximum contractile response, typifies surmountable blockade. Insurmountable blockade is manifested by major depressions in maximum contractile response.[15]

Candesartan, valsartan, and telmisartan are insurmountable AT_1 receptor antagonists.[12, 15–17] Eprosartan and losartan exert surmountable antagonism of the AT_1 receptor.[5, 18, 19] Data on the antagonistic binding of irbesartan and EXP-3174, the active metabolite of losartan, appear to be less conclusive. In one study, irbesartan had surmountable blockade of the AT_1 receptor.[15] In a different study, it shifted the concentration-response curve to the right in a parallel direction and caused a 20% decrease in maximum contractile response.[20] In addition, EXP-3174 displayed the mixed pattern antagonism of irbesartan. For example, it shifted the concentration-response curve to the right, together with 15% attenuation in maximum contractile response.[15] Whether insurmountable antagonism provides superior protection from angiotensin II is not known.

Hepatic Activation

Losartan undergoes biotransformation through cytochrome P450 (CYP) 2C9 and CYP3A4 isoenzymes to form the active metabolite EXP-3174.[5, 16, 18, 21–23] The metabolite has 10- to 40-fold greater potency than the parent drug and is believed to be responsible for most angiotensin II antagonism.[3, 5] Candesartan cilexetil is a prodrug but is activated to candesartan in the small intestine and thus is not primarily dependent on hepatic activation.[16]

Pharmacokinetic Differences

Absorption

All ARBs have a wide range of oral bioavailability, ranging from the lowest of 13% for eprosartan to the highest of 60–80% for irbesartan. Such differences are unlikely to be of clinical significance.[12, 16, 21–25] In addition, oral bioavailability of all ARBs is unaffected by food[12, 16, 21–25] so the drugs can be taken without regard to meals.

Metabolism and Elimination

In general, most ARBs are eliminated as unchanged parent drugs through the kidneys and bile.[12, 16, 21–25] Exceptions are losartan and irbesartan. The CYP3A4 and CYP2C9 isoenzymes metabolize losartan to active and inactive metabolites; fecal and urinary recovery rates of the drug approximate 60% and 35%, respectively.[12, 24] Irbesartan is metabolized primarily by the CYP2C9 isoenzyme to inactive metabolites; biliary elimination of the drug and its metabolites predominates over renal elimination; a combination of parent drug and inactive metabolites make up a fecal recovery rate of 80%.[22] Candesartan cilexetil undergoes biotransformation to candesartan and then to the inactive metabolite CV15959.[16]

No ARB requires dosage adjustment in patients with renal impairment.[12, 16, 21, 22, 24, 25] However, losartan requires an adjustment in those with hepatic impairment.[24] In a study of losartan in patients with normal hepatic function and those with mild to moderate alcoholic cirrhosis, the latter had 50% lower total clearance and a 5-fold increase in plasma concentration. Consequently, the manufacturer recommends lowering the initial losartan dose by 50% in patients with impaired hepatic function.[12, 24]

Onset of Action, Maximum Blood Pressure Effects, and Duration of Action

The ARBs share similar onset in blood pressure-lowering effects, approximately 2 hours after an oral dose.[17, 26–29] They tend to exert maximum antihypertensive effects approximately 6 hours after a dose.[17, 29–33] All six ARBs maintain their antihypertensive effect for at least 24 hours, thus allowing once-daily dosing.[23, 26, 31–34]

Dialyzability

The effect of hemodialysis on all ARBs is negligible. Despite lack of clinical data on hemodialysis extraction rates for valsartan, the manufacturer (product information reference in Micromedex) states that since the drug is highly protein bound (85–99%), hemodialysis clearance is unlikely to be of significance.[16, 21, 24, 25] No information on the effect of peritoneal dialysis on ARBs is available.

Drug Interactions

Only losartan and telmisartan have been shown to have potentially significant drug interactions.[16, 23, 24, 35–37] Telmisartan increased peak and trough plasma digoxin concentrations by 49% and 20%, respectively.[23, 24] Because a 49% increase in serum digoxin concentrations can cause the average patient with a baseline serum concentration of 1.4 ng/ml to exceed the therapeutic range (0.5–2 ng/ml), monitoring patients receiving the drug is prudent when telmisartan is begun. Because losartan undergoes CYP2C9- and CYP3A4-mediated oxidative metabolism, much attention has been focused on potential drug interactions. Until recently, much of the information on losartan and EXP-3174 pharmacokinetics came from in vitro experiments. Two small in vivo studies showed that the CYP2C9 metabolic pathway probably plays a prominent role in the agent's metabolism.[36, 37]

One study compared the effects of fluconazole, which preferentially inhibits CYP2C9 over CYP3A4 (in vitro), with itraconazole, a more selective CYP3A4 inhibitor, on the pharmacokinetics of losartan and EXP-3174 in normotensive subjects. Fluconazole doubled the half-life of EXP-3174 and decreased its area under the curve (AUC) and mean peak plasma concentration (C_{max}) by 47% and 30%, respectively.[37] In general, a 30% change in AUC is considered to be the minimum required to induce a clinically significant effect.[38] In contrast, fluconazole did not significantly alter pharmacokinetic variables of losartan. Itraconazole had no effect on losartan or EXP-3174 pharmacokinetics. Hence CYP2C9 inhibition by fluconazole exerted a dual effect by causing attenuating EXP-3174 formation and elimination.[37]

The effects of erythromycin and rifampin on losartan and EXP-3174 pharmacokinetics were examined in normotensive subjects. Erythromycin is a moderate CYP3A4 inhibitor, and rifampin induces CYP1A2, CYP2C, CYP3A4, and UDP glucuronosyl transferase.[36, 39] Rifampin decreased the AUCs of losartan and EXP-3174 by 35% and

40%, respectively. It decreased the half-life of EXP-3174 and did not significantly change the C_{max} of drug or metabolite. Pharmacokinetics of losartan and EXP-3174 remained unchanged after combination therapy with erythromycin and losartan. The investigators arrived at two conclusions. First, they speculated that the decreased AUC of losartan resulted from enhanced activation to EXP-3174 by the CYP2C9 pathway; and second, rifampin may have reduced the AUC of EXP-3174 by increasing its elimination through the UDP glucuronosyl transferase pathway. Future research should target the pharmacodynamic consequences of losartan drug interactions in hypertensive patients. Until then, one should anticipate the possibility of decreased therapeutic effects when coadministering losartan with rifampin or fluconazole.

Despite the potential for drug interactions with irbesartan, only one CYP2C9 inhibitor is reported to affect its metabolism: an in vitro study identified nifedipine as having the capacity to inhibit its CYP2C9-mediated oxidation.[40] Nifedipine had an inhibition rate constant of 20 μM. Whether such an interaction will have clinically significant effects remains to be seen.[24, 40] Because candesartan undergoes minimal CYP2C9 biotransformation, it is unlikely to interact with CYP2C9 inhibitors or inducers.[16] To date, drug interaction studies with warfarin (CYP2C9 substrate) and nifedipine (possible CYP2C9 inhibitor) show that pharmacokinetic variables (C_{max}, AUC) of candesartan were unaffected.[41]

Therapeutic Differences

Hypertension

Over the past few years investigators attempted to elucidate dose-response curves for ARBs. The prototypical study used trough diastolic blood pressure reductions from baseline as the primary efficacy variable. In general, blood pressure differences exceeding 2 mm Hg indicate clinically significant differences in antihypertensive effect.[42] Losartan, valsartan, and telmisartan have relatively shallow dose-response curves.[17, 43–48]

Losartan 10–50 mg once/day led to dose-dependent reductions in trough diastolic blood pressure. The dose-response curve attained a plateau at 50 mg once/day.[43, 44] Of interest, one ambulatory blood pressure-monitoring study compared the antihypertensive effects of losartan 50 mg once/day, 100 mg once/day, and 50 mg twice/day.[45] After 4 weeks, losartan twice/day exerted a 3.4-mm Hg greater decrease in mean diastolic blood pressure than 50 mg once/day ($p \leq 0.01$). Losartan 100 mg once/day caused a further decrease of 1.5 mm Hg compared with 50 mg once/day; the difference did not approach statistical significance. Consequently, patients unresponsive to an initial dosage of 50 mg once/day may benefit more from increasing the dosage to 50 mg twice/day than by taking 100 mg once/day.

Valsartan 10–80 mg induces dose-dependent reductions in trough diastolic blood pressure. Increasing the dose above 80 mg produced small increments in blood pressure lowering (< 2 mm Hg).[46, 47] Telmisartan has modest dose-dependent antihypertensive efficacy after increasing the dose from 20–40 mg. A plateau is achieved at 40–80 mg.[17, 48]

Irbesartan and candesartan appear to have greater dose-dependent antihypertensive effects than losartan, valsartan, and telmisartan.[22, 49–51] In one study irbesartan 50–75, 100–200, and 300 mg once/day caused reductions from baseline trough diastolic pressure of 6–8, 8.5–11.5, and 11.5–13 mm Hg, respectively.[22] An ambulatory blood pressure-monitoring study reported that no additional increase in antihypertensive efficacy resulted from giving irbesartan twice/day as opposed to once/day.[22] A study evaluating the dose-response effect of candesartan 2–32 mg once/day revealed a relatively shallow dose-response curve at doses ranging from 2–8 mg. A sharp increase in the reduction from baseline trough diastolic pressure occurred in the 16- to 32-mg interval, with a difference of 2.4 mm Hg between these doses.[49]

Only one study has evaluated the dose-response curve of eprosartan once/day. After 8 weeks of therapy, eprosartan 400, 600, 800, and 1200 mg caused reductions from placebo trough diastolic pressures of 1.9, 3.2, 2.7, and 4.3, respectively. Since only 600 and 1200 mg induced significant reductions from baseline compared with placebo ($p=0.01$ and $p=0.001$, respectively), the manufacturer recommended a starting dosage of 600 mg once/day.[31]

In general, the blood pressure-lowering effects of ARBs are similar to those of ACE inhibitors, dihydropyridine calcium channel blockers, and β_1-selective antagonists.[16, 23, 42–44, 48, 52–55] Within the past few years several studies compared the antihypertensive effects of various ARBs; for example, losartan was compared with irbesartan, candesartan, and telmisartan.[23, 54, 55] One study evaluated the effects of losartan 100 mg,

Table 1. Comparison of Angiotensin II Receptor Antagonists

	Losartan	Valsartan	Irbesartan	Candesartan	Telmisartan	Eprosartan
Dosing frequency[24, 31]	q.d. or b.i.d.	q.d.	q.d.	q.d. or b.i.d.	q.d.	q.d.
Food-drug interaction[12, 16, 21–25]	No	No	No	No	No	No
Drug-drug interaction[16, 23, 24, 35–37]	Rifampin, fluconazole				Digoxin	
Prodrug[5, 16, 18, 21–23]	No	No	No	Candesartan cilexetil	No	No
Active metabolite[5, 16, 18, 21–23]	EXP3174	No	No	Candesartan	No	No
Elimination[12, 16, 21–25]						
Fecal (%)	60	83	80	67	> 98	90
Urinary (%)	35	13	20	33		7
Dosage adjustment						
Cl_{cr} < 30 ml/min[24, 25]	No	No	No	No	No	No
Hepatic failure[24, 25]	↓ initial dose by 50%	No	No	No	No	No
Onset of BP effect (hrs)[17, 26–29]	2–3	2	2	2–4	3	No data
Maximum BP effect (hrs)[17, 29–33]	6	4–6	3–6	6–8	3–9	3
Hemodialyzable[16, 24, 25]	No	No	No	No	No	No
Initial dosage (mg/day)[24, 31]	50	80	150	8–16	40	600
Maintenance dosage (mg/day)[24, 31]	50–100	80–320	150–300	8–32	20–80	600–?
Dose-response plateau (mg)[17, 22, 41, 42, 44–49]	50	80	300	32	40–80	No data
T:P ratio[a] (%)[16, 17, 30, 31, 43, 47, 54]	58–78 (50–100 mg)	69–76[a] (80–160 mg)	> 60 (≥ 150 mg)	80 (8–16 mg)	≥ 97 (20–80 mg)	67 (600 mg)
Equivalent dosage (mg)	50	80	150	8	40	No data

[a]T:P ratio data from Novartis; numbers in parentheses represent dose range that corresponded to T:P ratio.

irbesartan 150 mg, and irbesartan 300 mg on trough diastolic blood pressure.[54] After 8 weeks, irbesartan 300 mg achieved a 3.0-mm Hg greater reduction than losartan 100 mg ($p<0.01$). No difference was detectable between irbesartan 150 mg and losartan 100 mg. Another study compared candesartan 8 and 16 mg and losartan 50 mg.[55] At 8 weeks, the trough diastolic pressure of patients receiving candesartan 16 mg was 3.7 mm Hg lower than that of patients receiving losartan 50 mg ($p=0.013$). The antihypertensive effect of candesartan 8 mg did not differ significantly from that of losartan 50 mg. An ambulatory blood pressure-monitoring study compared the antihypertensive effects of telmisartan 40 and 80 mg once/day with losartan 50 mg once/day.[23] After 6 weeks, both dosages of telmisartan reduced diastolic blood pressure more effectively than losartan during the final 6 hours of the 24-hour dosing interval ($p\leq0.05$).

All FDA-approved ARBs have trough:peak (T:P) ratios in excess of 50% for once/day dosing.[16, 17, 30, 31, 45, 49, 56] The ratio is calculated by dividing trough blood pressure by peak blood pressure drop within the dosing interval. A T:P ratio greater than 50% signifies the suitability of once-daily dosing, since the trough antihypertensive effect is less likely to be a residual of a large peak effect.[2]

Because comparative studies used inconsistent blood pressure-monitoring techniques and different dosage titration schedules, the ability to establish accurate dosage equivalence among ARBs is limited. Bearing that in mind, a general dosage equivalence scheme is shown in Table 1, together with other differences among the drugs.

Heart Failure

No ARBs are FDA approved for treating chronic heart failure.[24] The impetus for investigating the agents in heart failure originated from the expectation that they would incorporate the beneficial effects of ACE inhibitors without inducing associated adverse effects. To date only three trials of ARBs in heart failure have been published. In the Evaluation of Losartan in the Elderly Study (ELITE I), 722 ACE inhibitor-naive patients aged 65 years and older, with New York Heart Association (NYHA) class II–IV heart failure, were randomized to receive either losartan or captopril.[57] Target daily doses were 50 and 150 mg, respectively. The primary end point was change in renal function (≥ 0.3 mg/dl rise in serum creatinine). The combined risk of

death and hospital admissions due to heart failure was a secondary end point. Other efficacy measures were total mortality and rate of hospital admission due to heart failure, myocardial infarction, or unstable angina. Results indicated no significant differences between losartan- and captopril-treated patients with regard to primary and secondary end points. However, when all-cause mortality and hospital admission rates were viewed separately, losartan was superior to captopril (p=0.035 and 0.014, respectively). Evaluating mortality separately was not a prespecified end point, and hence this study alludes to the benefit of the ARB but does not prove its superiority over ACE inhibition. In addition, it should be emphasized that the absolute number of deaths in the study was small.[58]

These intriguing results led to ELITE II in which 3152 patients aged 60 years and older, with NYHA class II–IV heart failure, were randomized to receive either losartan or captopril.[59] Target daily doses of losartan and captopril were 50 mg and 150 mg (50 mg 3 times/day), respectively. The primary end point was all-cause mortality; the secondary end point was combined risk of sudden death and resuscitated cardiac arrest. Other end points were combined risks of all-cause mortality and hospitalizations, and cardiovascular mortality and hospitalizations. No significant differences were noted between treatment groups with regard to primary and secondary end points (results presented at the American Heart Association meeting, Atlanta, GA, November 10, 1999). However, the difference in the combined risk of sudden cardiac death and resuscitated cardiac arrest approached significance (p=0.08), with a trend favoring captopril. Since the withdrawal rate was significantly lower in the losartan group compared with the captopril group (p=0.001), it is anticipated that losartan may be indicated for patients with heart failure who are intolerant of ACE inhibitors.

In phase I of the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study, 768 patients with NYHA class II–IV heart failure were randomized to receive either monotherapy or combination therapy for 43 weeks.[60] Monotherapy regimens consisted of various doses of candesartan once/day. Combination therapy included various dosages of candesartan and enalapril. The primary end point was exercise tolerance. Interim analysis of data by the External Safety and Efficacy Monitoring Committee resulted in premature termination of the study. The committee judged candesartan monotherapy twice/day and combination therapy to be less efficacious than enalapril twice/day in improving exercise tolerance.

Two other trials evaluating ARBs in treating heart failure are in progress.[61] The Candesartan Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) will enroll approximately 6500 patients worldwide (personal communication, Astra Pharmaceuticals, 1999). Treatments are candesartan monotherapy in ACE inhibitor-intolerant patients, combination therapy with an ACE inhibitor, and candesartan monotherapy in patients with ejection fractions surpassing 40%.[60] The Valsartan Heart Failure Trial (Val-HeFT) will investigate the agent's effect on morbidity and mortality in approximately 5000 patients with NYHA class II–IV disease. Patients will be randomized to treatment with valsartan 160 mg twice/day or placebo.[61] They also will receive standard therapy.

Future Directions

Two trials are studying the effects of losartan and valsartan in patients after acute myocardial infarction. In the Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial, approximately 5000 patients aged 50 years and older will be randomized to receive the ARB or captopril.[62] The primary end point is all-cause mortality. The study will continue until 937 deaths occur. The Valsartan in Acute Myocardial Infarction (VALIANT) trial also is planned.[63]

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) study enrolled 500 severely hypertensive patients after acute ischemic stroke.[64] The primary end point is morbidity and mortality 3 months after the stroke.

Diuretics and β-blockers are the only antihypertensive drugs known to reduce mortality in hypertensive patients.[65] In a subset analysis of diabetes in the Systolic Hypertension in Europe trial, nitrendipine, a dihydropyridine calcium channel blocker, reduced overall mortality by 55% (p=0.04).[66] Two ongoing trials are assessing the effects of losartan and valsartan on cardiovascular morbidity and mortality. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study enrolled 9194 patients aged 55–80 years.[67] The primary end

point encompasses events such as cardiovascular death, acute myocardial infarction, and nonfatal cerebral stroke. The study will compare the effects of losartan and atenolol monotherapy on cardiovascular morbidity and mortality and will continue until 1040 patients achieve the primary end point. The Valsartan Antihypertensive Long-term-use Evaluation (VALUE) trial will compare the effects of valsartan and amlodipine monotherapy on cardiovascular morbidity and mortality in 14,400 patients.[68] It will continue for 4 years or until 1450 patients experience the primary end point.

Less well-documented applications of losartan include treatment of posttransplantation proteinuria, posttransplantation erythrocytosis, and primary Raynaud's phenomenon. After 1 year of treatment with losartan 50 mg once/day, a renal transplant recipient progressed from having a urinary protein excretion rate of 3.4 g/day to negative urinary protein excretion.[69] Case reports of patients with posttransplantation erythrocytosis indicated that within 3 months of starting losartan, hemoglobin and hematocrit levels decreased by approximately 2.3 g/dl and 9%, respectively.[70] The drug appears to reduce the frequency of vasospastic crises in patients with primary Raynaud's phenomenon.[71]

Summary

In the past few years the ARB class of drugs has expanded considerably. Since losartan relies on the CYP3A4 and CYP2C9 oxidative pathways to form its active metabolite EXP-3174, an alternative ARB should be considered for hepatically impaired patients. Due to the risk of attenuation in blood pressure-lowering effects, patients taking losartan and fluconazole or rifampin should have blood pressure monitored frequently. The only other potentially important drug interaction is between telmisartan and digoxin. Patients with inadequate blood pressure control with losartan 50 mg once/day may benefit more from titrating to 50 mg twice/day rather than 100 mg once/day.

Relatively few studies directly compared antihypertensive effects among the ARBs. The most extensively studied are losartan, irbesartan, and candesartan. Comparative studies show losartan 50–100 mg once/day to be less efficacious than high-dose irbesartan 300 mg or moderate-dose candesartan 16 mg once/day. Unlike irbesartan and candesartan, losartan has a flat dose-response curve above 50 mg when given once/day. Whether or not higher-dose irbesartan and candesartan are superior to losartan 50 mg twice/day has yet to be established.

Of interest, telmisartan, one of the newer agents in the class, provided superior antihypertensive effects during the final 6 hours of the 24-hour dosing interval compared with losartan once/day. Telmisartan also has a flat dose-response curve when given once/day. Larger comparative trials will determine the validity of early results.

To date, the only FDA-approved indication for ARBs is treatment of hypertension. Results from continuing trials will provide insight on their future role in treatment of congestive heart failure, myocardial infarction, and cerebral stroke.

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